



Attorney's Docket No. 015200-054

#21/E
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Patent
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(NE)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RECEIVED

In re Patent Application of)

AMMON et al)

Application No.: 09/011,977)

Filed: June 15, 1998)

For: USE OF BOSWELLIC ACID AND)
ITS DERIVATIVES FOR)
INHIBITING NORMAL AND)
INCREASED LEUCOCYTIC)
ELASTASE OR PLASMIN)
ACTIVITY)

Group Art Unit: 1623

Examiner: H. Owens Jr.

JAN 18 2002

TECH CENTER 1600/2900

REPLY

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In complete response to the Official Action mailed on July 12, 2001, applicants provide the following remarks. In accordance with Examiner Owens facsimile of October 12, this Official Action is **NON-FINAL**. Reexamination and further and favorable reconsideration of the above-identified application, in view of the following remarks, is respectfully requested.

Initially, applicants note that in accordance with the telephonic interview with the Examiner, conducted on October 10, 2001, the Official Action is **non-final**.

Claims 10, 12-22, 24-25 and 27 have been rejected under 35 U.S.C. § 103(a) for purportedly being obvious over Ammon et al (EP 0 552 657) in combination with Mulshine

et al (WO 95/24894) and Han (*Chin. Med. Sci. J.* 9(1):61-69 (1994)). For at least all of the reasons set forth below, withdrawal of this rejection is believed to be in order.

The present invention is drawn to methods of combating serious diseases, such as pulmonary emphysema, acute respiratory distress syndrome, shock lung, cystic fibrosis, chronic bronchitis, glomerulonephritis, rheumatoid arthritis, and for combating tumors and neoplasms or tumor metastases. The diseases and tumors to be treated by the present invention are caused by increased plasmin activity or can be treated by the inhibition of normal leucocytic elastase or plasmin activity. The methods of the present invention comprise administering an effective amount of boswellic acid, a physiologically acceptable salt, a derivative, a salt of the derivative, a plant extract containing boswellic acid, or combinations thereof.

As noted in the specification, the inhibition of leucocytic elastase is important because during the pathophysiological processes of the diseases being treated, this enzyme (which is released from activated neutrophilic granulocytes) plays an important part in the destruction of functional tissue. Thus, the aim of the present invention is to block the final destruction of tissues and organs resulting from the indicated diseases. It was not previously known that boswellic acid could be used for such a purpose.

In the prior art, 5-lipoxygenase inhibitors, such as boswellic acids, had only been claimed to be useful for treating mild to moderate diseases, such as asthma. There was no indication in the prior art that 5-lipoxygenase inhibitors could be used to treat serious diseases, such as those treated by the present invention.

Ammon et al disclose the use of boswellic acid compounds for treating influencing inflammation in diseases by inhibiting leukotriene synthesis. Although Ammon et al lists among the diseases to be treated "diseases of the joints (rheumatism)", applicants note that rheumatoid arthritis (which is treated by the present invention) is very different from other rheumatoid diseases. Rheumatoid arthritis is based on the destruction of the articular cartilage, in contrast to other rheumatoid diseases. This destruction leads to an irreversible deformation of the joint which hinders movement. The destruction of the articular cartilage is not prevented by other drugs for the treatment of rheumatoid arthritis, such as inhibitors of cyclooxygenase or 5-lipoxygenase.

Thus, although Ammon et al may disclose the use of boswellic acid for influencing inflammation, such a disclosure would not suggest the present invention, which uses boswellic acid for combating more serious diseases and conditions caused by an increase in leucocytic elastase or plasmin activity.

Mulshine et al discloses that lipoxygenase inhibitors, i.e. inhibitors of 5-lipoxygenase, can be used to treat epithelial cell-derived cancer. Please see the attached table (Exhibit A) which summarizes the disclosure of Mulshine et al in terms of what concentrations of the 5-lipoxygenase inhibitors are required for there to be cytotoxic activity. Further effects of these inhibitors outside of 5-lipoxygenase inhibition are indicated as well (in other words, these compounds are not just inhibitors of 5-lipoxygenase).

This table shows that three different 5-lipoxygenase inhibitors (AA-861, NDGA and MK-886) exert cytotoxic actions in tumor cells. However, there is no evidence from the

data presented that the 5-lipoxygenase inhibition function of each of these compounds is the rational for their capacity to kill epithelial cells. Moreover, the postulated mechanism of action (cell toxicity due to 5-lipoxygenase inhibition) is likely not to be the correct rational for two reasons. (1) All three of the 5-lipoxygenase inhibitors not only inhibit 5-lipoxygenase, but also impair or induce other enzymes and cell regulatory functions. Each of these alternative actions, which are not related to the 5-lipoxygenase inhibition, is sufficient to cause the cytotoxic (antiproliferative/antitumor/anticancer) effects. (2) Mulshine et al show cell toxicity at about 10 μ M of the compounds. These concentrations are about 100 to 1000 times higher than the concentrations needed for the inhibition of 5-lipoxygenase activity, as shown in the following table.

| Compound | Inhibition of 5-lipoxygenase | Inhibition of tumor growth |
|----------|------------------------------|----------------------------|
| AA-861 | 0.1-0.8 μ M | \geq 5-10 μ M |
| NDGA | 0.25-0.51 μ M | \geq 10 μ M |
| NK-886 | 10-14 μ M | \geq 5 μ M |

That three compounds, which happen to inhibit 5-lipoxygenase synthesis, kill tumor cells (at substantially higher concentrations than required to inhibit 5-lipoxygenase) does not mean that 5-lipoxygenase inhibition is the rational for the potential of these compounds to reduce tumor cell growth. It could just as easily be their ability to mobilize Ca^{2+} , or to inhibit COX (cyclooxygenase). In fact, the differences in the concentrations needed for 5-lipoxygenase inhibition and for cell growth reduction would suggest that there are two

different mechanisms of action for each of these compounds: one for the inhibition of the enzymatic activity of 5-lipoxygenase and one for cytotoxicity.

Thus, although boswellic acid is a 5-lipoxygenase inhibitor, there is no evidence provided by Mulshine et al to suggest that all 5-lipoxygenase inhibitors, including boswellic acid, could be used to combat tumors.

Furthermore, Han does not disclose or suggest the present invention. Han discloses that the differentiation of HL-60 cells is induced by boswellic acid. According to the present invention, however, a limitation of the tumor mass and an inhibition of the formation of metastases is intended. Increased differentiation of tumor cells cannot be equated with the limitation of the tumor mass, as is claimed by the present invention, nor can it be equated with the inhibition of the formation of metastases. Therefore, Han does not disclose or suggest the present invention.

In light of these remarks, applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

CONCLUSION

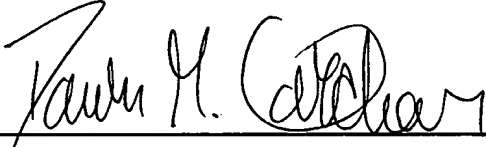
From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

In the event that there are any questions relating to this application, the Examiner is invited to telephone the undersigned so that prosecution of the subject application may be expedited.

Respectfully submitted,

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